Tetrahedron: *Asymmetry* 21 (2010) 2542–2549

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

A practical procedure for the removal of the phenylethanol moiety from phenylglycinol-derived lactams

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ARTICLE INFO

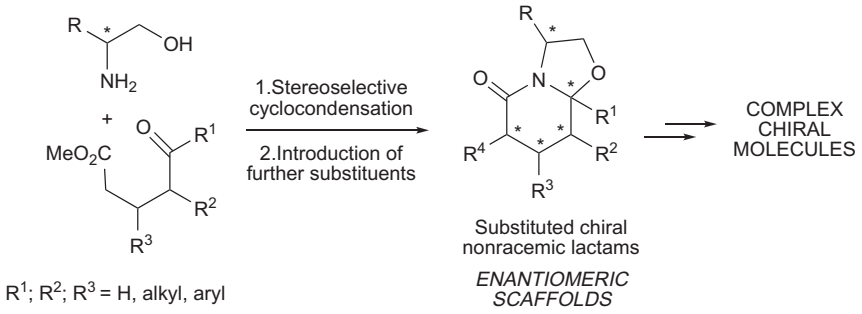
Article history:
Received 14 September 2010
Accepted 29 September 2010
Available online 26 October 2010

ABSTRACT

Chiral non-racemic bicyclic lactams derived from phenylglycinol have been appointed as key building blocks for the preparation of enantiopure nitrogen compounds. The removal of the chiral inductor leading to substituted piperidones by using air or oxygen in basic media is presented.

1. Introduction

Chiral aminoalcohol-derived bicyclic lactams[1] are considered as an outstanding example of organic enantiomeric scaffolds[2] for the enantiocontrolled synthesis of complex molecules. These compounds are easily accessible via cyclocondensation reactions of racemic or prochiral δ-oxo(di)acid derivatives with chiral nonracemic amino alcohols. Amongst them, phenylglycinol-derived oxazolopiperidone lactams (R = Ph) are exceptionally versatile building blocks for the enantioselective construction of structurally diverse piperidine-containing natural products and bioactive compounds (Scheme 1).[3]



Scheme 1. General strategy.

Typically, bicyclic lactams with the general structure **A** are transformed into enantiopure polysubstituted 2-piperidones by removing the chiral inductor in two steps: (1) opening of the oxazolidine ring, which is accomplished either by an α-amidoalkylation reaction involving the introduction of a substituent at the α-position, or by reductive treatment with Et_3SiH in the presence of a Lewis acid ($TiCl_4$); and (2) debenzylation by treatment under dissolving metal conditions (sodium in liquid ammonia)[4] or multistep processes.[5] This methodology provides versatile diversely substituted enantiopure piperidones, which are key intermediates in the construction of nitrogen compounds (Scheme 2).

Alternatively, removal of the chiral inductor to afford piperidine derivatives can be performed by the initial reduction ($LiAlH_4$, BH_3, etc.) of the lactam carbonyl followed by debenzylation by hydrogenolysis.[3]

Conventional Birch debenzylation reductions[6] are performed with alkali metals in liquid ammonia at −33 °C. Despite its utility, this method has several undesirable drawbacks that limit its use, particularly on a large scale,[7] such as the inherent dangers of handling elemental alkali metals and the toxicity of ammonia, and also the nuisance and hazards of running cryogenic reactions.[8] Moreover, in the particular case of phenylglycinol-derived lactams, the

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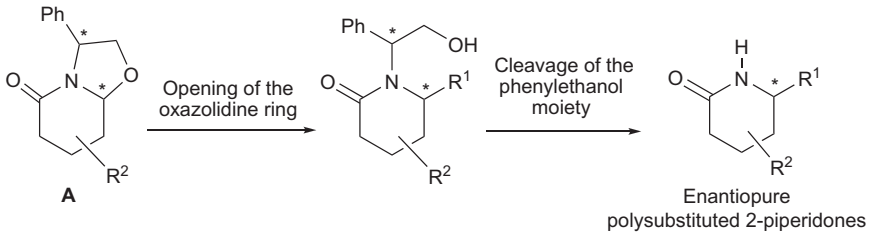
doi:10.1016/j.tetasy.2010.09.014



Scheme 2. Steps to remove the chiral inductor from lactams **A**.

crude reaction mixture after the aqueous work-up contains phenylethanol, which has to be separated from the final N-unsubstituted piperidones by column chromatography.

In 1983, Gigg reported the use of potassium *tert*-butoxide/DMSO and O_2 for the rapid *N*-debenzylation of nitrogen-functionalized glucopyranosides.[9] Nearly twenty years later, the same reagents in the hands of Deaton–Rewolinski allowed the *N*-debenzylation of aromatic heterocycles.[10] Simultaneously, a novel and efficient oxidation of 1,2-aminoalcohols to dialkylamides with potassium hydroxide under aerobic conditions was accomplished by Pedrosa.[11]

Inspired by this previous work, and in an effort to avoid the drawbacks of using sodium in ammonia or multistep sequences, we herein report an easy, safe and cost-effective procedure for the removal of the 2-hydroxy-1-phenylethyl moiety from the phenylglycinol chiral auxiliary in chiral oxazolopiperidone bicyclic lactams. Essentially, it consists of the use of oxygen as an oxidant under basic conditions.

2. Results and discussion

2.1. Preparation of *N*-(2-hydroxy-1-phenylethyl)-2-piperidones 5–10

Enantiopure lactams *cis*-**1** and *cis*-**2** are easily accessible by cyclocondensation of (*S*)-phenylglycinol with methyl 5-oxopentanoate[12] or methyl 4-formylhexanoate,[13] respectively, under neutral conditions. Isomerization of *cis*-**1** and *cis*-**2** under acidic conditions gave access to H-3/H-8a trans lactams *trans*-**1**[12] and *trans*-**2**,[4d] respectively (Scheme 3).

In order to study the scope of the proposed debenzylation reaction, a variety of diversely substituted *N*-(2-hydroxy-1-phenylethyl)-2-piperidones were prepared by diastereoselective enolate alkylation and/or α-amidoalkylation procedures, following the experimental conditions previously described by our group.

In previous studies all attempts to carry out α-amidoalkylation reactions from lactams *cis*-**1** or *cis*-**2** have been unsuccessful. In all cases, only the starting material was recovered, thus confirming the reluctance of *cis* H3–H8a phenylglycinol-derived lactams to undergo α-amidoalkylation reactions.[14] However, the opening of the oxazolidine ring in lactams with a *trans* relationship between H-3/H-8a has been performed easily. Thus, *trans*-**1** and *trans*-**2** lactams were chosen as starting materials.

The diastereoselective alkylation of non-substituted oxazolopiperidone *trans*-**1** with EtI gave exclusively α-ethyl substituted oxazolopiperidone **3**,[12a] and the dialkylation reaction with allylbromide led to bicyclic lactam **4**.[15]

By choosing the appropriate organometallic reagent, the stereocontrolled formation of a C–C bond at the C-6 position of the piperidone can be ensured.[14] The opening of the oxazolidine ring by Grignard reagents (MeMgBr and PhMgBr) from *trans*-**1** took place stereoselectively with retention of configuration at the C-8a stereocentre, to afford the corresponding compounds **5** and **6**.[14] The reaction of *trans*-**1** with indole in the presence of $TiCl_4$ led to a 3:1 mixture of 6-(3-indolyl)-2-piperidones **7** and 6-*epi*-**7**. The *N*-MEM-indole derivative **7a** was prepared from **7** by silylation of the hydroxy group, followed by reaction with MEMCl, and desilylation with TBAF (73% overall yield).[16]

The stereochemical outcome changed when a Lewis acid such as $TiCl_4$ was used, and introduction of allyltrimethylsilane to *trans*-**2** and **3** took place with inversion of the configuration at the C-8a stereocenter to give the respective *cis*-5,6-disubstituted piperidone **8** and 3,6-disubstituted piperidone **9**.

Finally, reductive cleavage of the C–O bond of the oxazolidine ring of **4** with Et_3SiH–$TiCl_4$ gave compound **10** in 78% yield (Scheme 4).

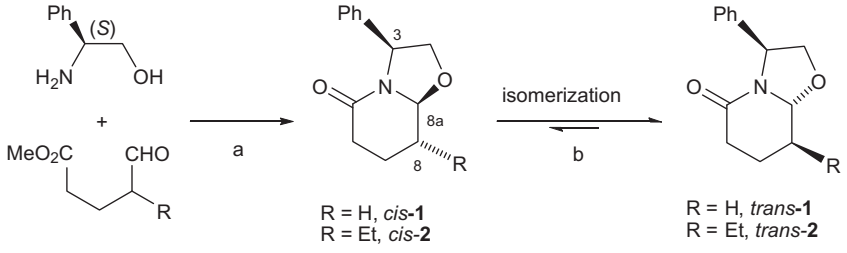
2.2. Debenzylation reaction of lactams 5–10

2.2.1. Reaction conditions

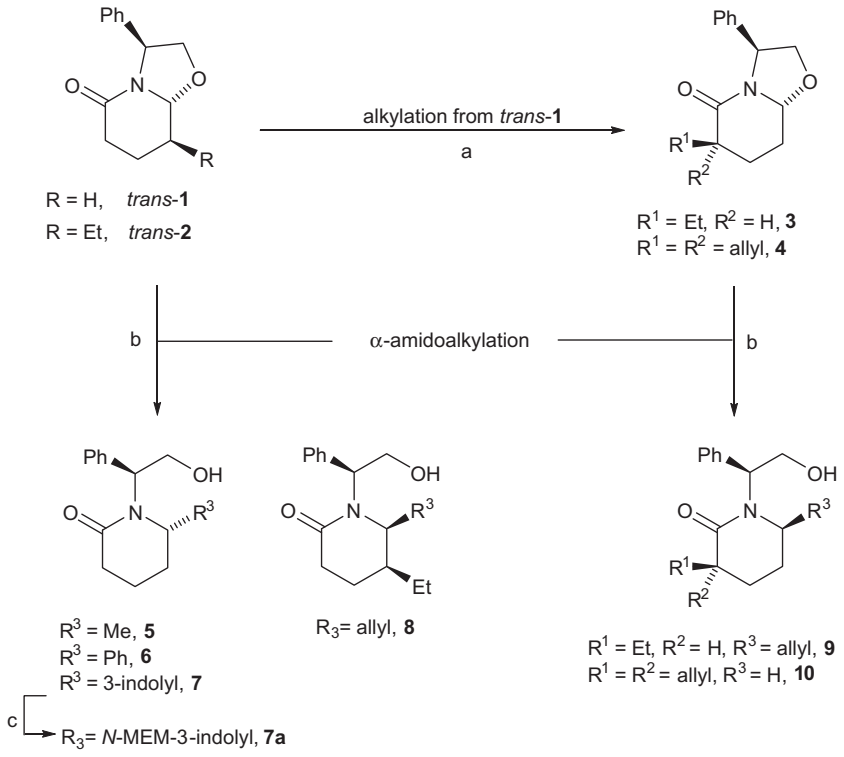
With a variety of diversely substituted *N*-(2-hydroxy-1-phenylethyl)-2-piperidones in hand, we first decided to set up new oxidative reaction conditions from the 5,6-*cis* disubstituted lactam **8** (Table 1).

To start with, we considered the conditions used by Pedrosa in the oxidation of amino alcohols and amino ketones to dialkylamides and carboxylic acids.[11] Treatment of **8** with an excess of KOH in Et_2O at room temperature under aerobic conditions led to **14** in 65% yield (entry 1), which increased to 80% under an oxygen atmosphere (entry 2). Remarkably, benzoic acid was formed in these reactions.

In order to fine tune the reaction conditions, we then studied possible modifications of different factors such as the base, solvent, atmosphere, and sun lamp/heating. As mentioned earlier, one of

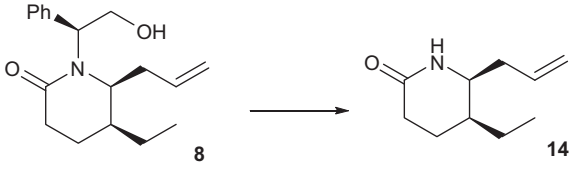


Scheme 3. Synthesis of the starting lactams. Reagents and conditions: (a) toluene, reflux, 36 h, 86%, *cis*-**1**/*trans*-**1** 85:15; toluene, reflux, 18 h, 80%, *cis*-**2**/*trans*-**2**/*epi*-**8**-*trans*-**2** 63:25:12; (b) TFA–CH_2Cl_2 64 h, 25 °C, from *cis*-**1**, 14:86 *cis*-**1**/*trans*-**1**; MeOH–HCl 3 M, 25 °C, 25 h, from *cis*-**2**, *cis*-**2**/*trans*-**2**/*epi*-**8**-*trans*-**2** 28:70:2.



Scheme 4. Synthesis of starting lactams. Reagents and conditions: (a) (i) LiHMDS, −78 °C, 1 h; (ii) EtI, 2 h, 83%, **3**; (b) MeMgBr, Et_2O, 0 °C, 8 h, 62%, **5**. PhMgBr, 0 °C, 8 h, 72%, **6**. Indole, $TiCl_4$, 25 °C, 30 min, 80%, 3:1, **7**: 6-*epi*-**7**. $AllylSiMe_3$, $TiCl_4$, CH_2Cl_2, rt, 23 h, 83%, **8**. $AllylSiMe_3$, $TiCl_4$, CH_2Cl_2, 0 °C, 2 h and rt, 16 h, 91%, **9**. Et_3SiH, $TiCl_4$, CH_2Cl_2, rt, 18 h, 78%, **10**; (c) (i) *t*$BuMe_2SiCl$, imidazole, DMF, 35 °C; (ii) KH, $ClCH_2OCH_3$, THF, 0 °C, 81%; (iii) Bu_4NF, THF, 4 h, rt, 90%, **7a**.

Table 1
Debenzylation conditions of lactam **8**



Entry	Base	Equiv	Solvent	Time (h)	Conditions	Yield (%)
1	KOH	50	Et_2O	16	Air, rt	65
2	KOH	50	Et_2O	16	O_2, rt	80
3	NaOH	50	THF	20	O_2, lamp[a]	60
4	NaOH	25	THF	24	O_2, lamp[a]	66
5	NaOH	25	PhMe	65	O_2, lamp[a]	49
6	NaOH	25	MTBE	22	O_2, lamp[a]	57
7	NaOH	25	MTBE	16	O_2, 40 °C	71
8	NaOH	10	MTBE	16	O_2, 40 °C	83
9	NaOH	5	MTBE	16	O_2, 40 °C	40
10	NaOH	10	MTBE	16	air, 40 °C	60[b]
11	NaOH	10	MTBE	16	O_2, rt	68[b]

[a] A 250 W sun lamp was used at 25 cm of the reaction flask.
[b] 27% of **8** was recovered (entry 10), 10% of **8** was recovered (entry 11).

our concerns was to develop a methodology that would tackle the scale-up problems of other debenzylation methods.

2.2.1.1. Base. The number of equivalents of the base and its solubility were improved by replacing KOH with NaOH and Et_2O with THF, respectively. Thus, when the reaction was carried out using NaOH as the base in THF under oxygen atmosphere in the presence of a sun lamp (20 h), the final product **14** was isolated in 60% yield (entry 3). Halving the NaOH (25 equiv) had no effect on the yield (entry 4).[17]

2.2.1.2. Solvent. As the use of Et_2O or THF under aerobic conditions can result in the formation of dangerous peroxides, other solvents such as toluene and *tert*-butylmethylether (MTBE) were tested.[18] The use of toluene required increasing the reaction time to 65 h to complete the conversion of **8** into the final product, with the yield being lower (49%) (entry 5).

In contrast, MTBE, which has a distinct advantage over most ethers in showing no tendency to form explosive organic peroxides, proved to be a good media for the debenzylation reaction (entry 6). Changes in the lactam concentration had no influence on the final yield.

2.2.1.3. Sun lamp/heat. Based on a previous work suggesting a radical mechanism in debenzylation reactions by oxidative procedures involving oxygen, we included a sun lamp in the above experimental process (entries 3–6).[19]

To determine if the heat provided by the sun lamp was the real accelerator, the following reactions were carried out at 40 °C in the dark (entries 7–11). Indeed, the new conditions gave a good yield (71%) of the pure final product (entry 7). Reduction of the excess of base to 10 equiv resulted in an 83% yield (entry 8), although a further reduction to 5 equiv resulted in a lower yield (entry 9).

When the reaction was carried out under aerobic conditions, 27% of the starting material was recovered (entry 10). At room temperature, the debenzylated product **14** was obtained in 68% yield, with recovery of 10% of the starting material **8** (entry 11).

From the above experiments, the best debenzylation conditions for lactam **8** were the use of NaOH (10 equiv) in MTBE as the solvent at 40 °C in the presence of oxygen (entry 8).

To compare these new debenzylation conditions with the Birch procedure, we subjected compound **8** to the Na/liquid NH_3 reaction conditions. The best yield (81%, **14**; 7%, **8**) was obtained when the reaction was performed at −33 °C starting from 1 g of **8**. When the

reaction was scaled up, the starting product **8** (3 g) was consumed but the formation of **14** was not observed.

The experimental conditions involved in the Na/liquid NH_3 methodology are somewhat difficult to control. For example, Na metal is added in small portions to a solution of the lactam in NH_3 until a blue colour persists, but as the surface of Na is rapidly damaged by the air, the quantities of metal used are variable. Moreover, the basic conditions can affect some functional groups.

In contrast, the reagents and conditions involved in the oxygen-mediated debenzylation reaction are controllable, the consumption of the starting material is easily monitored by TLC and the reaction can be carried out on a multigram scale.

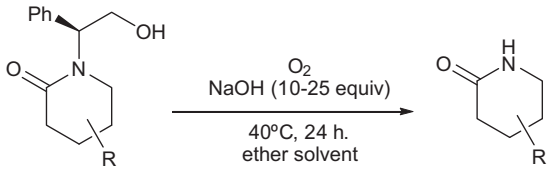
2.2.2. Debenzylation of lactams 5–10

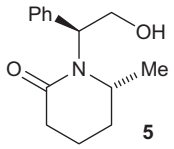
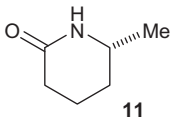
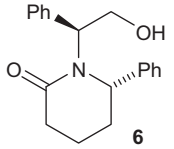
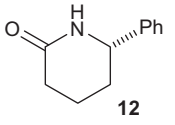
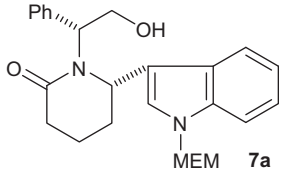
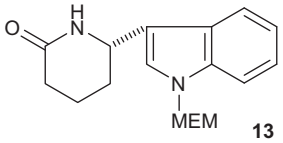
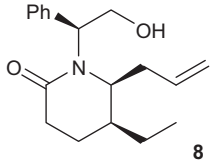
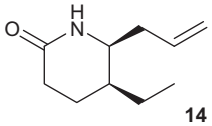
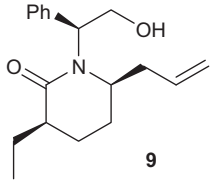
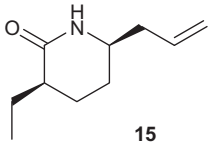
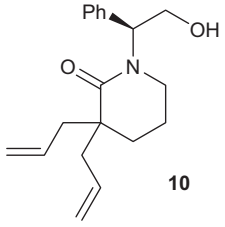
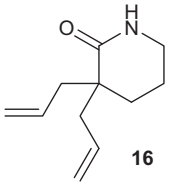
With the aim of evaluating the scope of the reaction, the cleavage of the 2-hydroxy-1-phenylethyl moiety in different substituted lactams **5**, **6**, **7a**, **9** and **10** was undertaken (Table 2).

When the 6-methyl substituted lactam **5** was treated under the standard basic oxidative conditions using THF or MTBE as the solvent, debenzylation occurred in good yield (87%) to give 6-methyl-2-piperidone **11** (entry 1). Notably, in some runs enamide **17** and imide **18** were formed in low yield (Scheme 5). These products are key intermediates to postulate the mechanism of the reaction (see Section 3).

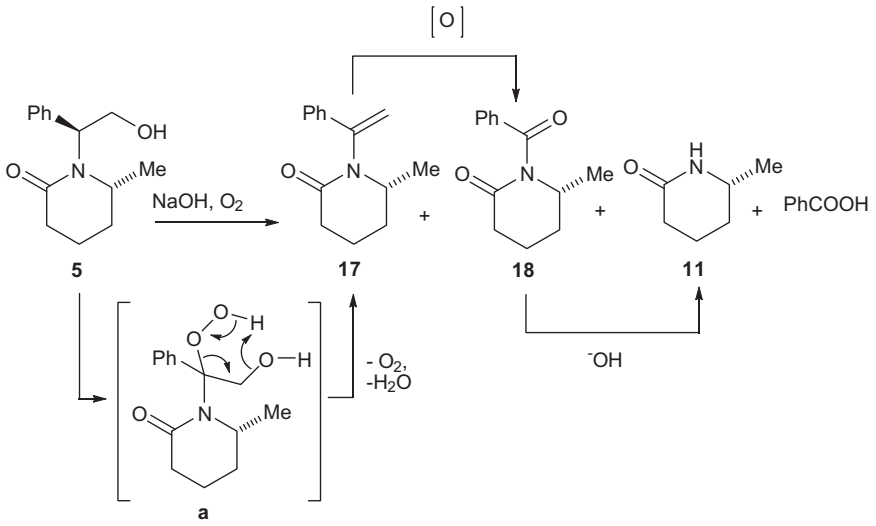
Similarly, 6-phenyl lactam **6** was transformed into **12** in good yield (entry 2; 81%). In this case THF was used as a solvent due

Table 2
Cleavage of the 2-hydroxy-1-phenylethyl moiety



Entry	Starting material	Product	Yield (%)
1	 **5**	 **11**	87
2	 **6**	 **12**	81
3	 **7a**	 **13**	72
4	 **8**	 **14**	85
5	 **9**	 **15**	89[a]
6	 **10**	 **16**	88

[a] Epimerization was observed at the C-3 position to furnish a 1:1 mixture of **15** and 3-*epi* **15**.



Scheme 5. Postulated mechanism of O_2/OH^- mediated debenzylation process.

to the low solubility of the starting material in MTBE. Notably, this transformation involves the chemoselective cleavage of the exocyclic *N*–CHPh bond.

When the reaction was performed from the 6-*N*-MEM-indolyl derivative **7a**, the N-unsubstituted lactam **13** was isolated in 72% yield (entry 3). Debenzylation from the N-unprotected indole derivative **7** was unsuccessful.

As mentioned above, the reaction of 5,6-*cis*-disubstituted lactam **8** (3 g) under standard conditions furnished **14** in 85% yield after 24 h (entry 4).

When 3,6-disubstituted lactam **9** was subjected to the standard debenzylation conditions, a 1:1 mixture of lactams **15** and 3-*epi*-**15** was obtained (entry 5). The same result was observed when the reaction was carried out at room temperature. Epimerization of lactam **15** occurred after treatment with base under an inert atmosphere, indicating the lability of the acidic proton. However, lactam **9** remained unchanged under the same conditions.

Finally, the debenzylation of 3,3-diallyl substituted derivative **10** gave **16** in 88% yield (entry 6).

3. Mechanistic considerations

When the reaction from **8** was conducted in the absence of oxygen or air, or when the base was not included in the experimental procedure, only the starting material was recovered; this demonstrates the crucial role that both factors play in the process.

As aforementioned, when the debenzylation of **5** was conducted in MTBE with 25 equiv of NaOH, enamide **17** was isolated as a by-product (6% yield)[20] and trace amounts of imide **18** were detected. The structure of **18** was confirmed unequivocally by comparison with an authentic sample prepared by acylation of N-unsubstituted lactam **11** with benzoyl chloride.[21]

It is well known that molecular oxygen can oxidize benzylic positions[22] so in the reaction of **5** an intermediate such as **a** could be considered. Extrusion of O_2 and H_2O from hydroperoxide **a** would furnish enamide **17**. Further oxidation of enamide **17** would give imide **18**,[23] which in turn would undergo hydrolysis under basic conditions to afford N-unsubstituted lactam **11** and benzoic acid (Scheme 5).

As an additional test, two different N-substituted lactams were examined. When either *N*-benzyl-2-piperidone or *N*-(2-hydroxyethyl)-2-piperidone was subjected to the $NaOH/O_2$ conditions described, only the starting material was recovered. Therefore, in support of the proposed mechanism, the *N*-2-hydroxyethyl-1-phenyl moiety was proven to be an essential structural requirement for the progress of the reaction.

4. Conclusion

In conclusion, as an alternative to classical Na/liquid NH_3 conditions, we have provided an environmentally friendly, easy to handle, and cost-effective method for cleaving the *N*-(2-hydroxy-1-phenyl)ethyl moiety from phenylglycinol-derived oxazolopiperidone lactams. Advantageously, air (diluted oxygen) or oxygen, which are the cheapest oxidants, was used without irradiation or catalysts. The reaction work-up only requires an acid-base extraction to eliminate the benzoic acid formed, and the desired debenzylated product can be used for synthetic purposes without further purification. Moreover, a putative mechanism for this transformation has been proposed based on the isolation of possible intermediates in the process.

5. Experimental

5.1. General

All non-aqueous reactions were performed under an inert atmosphere with dry, freshly distilled solvents using standard procedures. Solvents for the debenzylation reaction (MTBE, Et_2O and PhMe) were used without purification. THF was distilled prior to use, to avoid possible interaction of BHT (antioxidant stabilizer). Commonly available hydroxides (NaOH, KOH) were used without any purification. Drying of organic extracts during the work-up of reactions was performed over anhydrous Na_2SO_4 or $MgSO_4$. Evaporation of solvents was accomplished with a rotatory evaporator. For reactions that need an oxygen atmosphere the flask was equipped with 1 gallon gas bag (heavy natural rubber, Aldrich Z186740). In experiments with irradiation, a commercial lamp (Philips POWERTONE, ML 250 W E40 225–235 V) was installed ca. 25 cm from the reaction flask. Thin layer chromatography was done on SiO_2 (Silica Gel 60 F_{254}) and the spots were located by UV or 1% $KMnO_4$ solution. Chromatography refers to flash column chromatography and was carried out on SiO_2 (Silica Gel 60, 230–400 mesh). Melting points were determined in a capillary tube and are uncorrected. Unless otherwise indicated, NMR spectra were recorded in $CDCl_3$ at 300 or 400 MHz (^1H) and 75.4 or 100.6 MHz (^{13}C), and chemical shifts are reported in δ values downfield from TMS or relative to residual chloroform (7.26 ,

77.0 ppm) as an internal standard. Data are reported in the following manner: chemical shift, multiplicity, coupling constant (J) in hertz (Hz), integrated intensity. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad signal.

5.2. (6*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-6-[1-(methoxymethyl)indol-3-yl]-piperidin-2-one 7a

TBAF (0.6 mL, 0.58 mmol, 1.0 M THF) was added dropwise to a solution of (6*S*)-1-[(1*R*)-(*tert*-butyldimethylsilyl)oxy-1-phenylethyl]-6-[1-(methoxymethyl)indol-3-yl]piperidin-2-one[16] (190 mg, 0.38 mmol) in THF (1 mL). The mixture was stirred at rt for 4 h. Then EtOAc and 0.5 M HCl solution were added to the reaction mixture. The organic phase was washed with brine, dried and concentrated. The residue was purified by column chromatography (EtOAc to 99:1 EtOAc–MeOH) to yield **7a** (131 mg, 90%). IR (KBr) 3386, 2944, 1621, 1465 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 1.67 (m, 1H, H-4), 1.80 (m, 1H, H-4), 2.01 (m, 1H, H-5), 2.11 (m, 1H, H-5), 2.56 (m, 1H, H-3), 2.70 (m, 1H, H-3), 3.27 (s, 3H, OCH_3), 3.98 (dap, J = 12.0 Hz, 1H, CH_2OH), 4.16 (dt, J = 12.0, 8.2 Hz, 1H, CH_2OH), 4.43 (br s, J = 6.8 Hz, 1H, CHPh), 4.83 (t, J = 4.0 Hz, 1H, H-6), 4.88 (br s, 1H, OH), 5.43 (s, 2H, NCH_2OMe), 7.10–7.19 (m, 2H, Hind), 7.23–7.34 (m, 6H, Hind), 7.44 (d, J = 7.9 Hz, 1H, H-7ind), 7.50 (d, J = 8.3 Hz, 1H, H-4ind); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.8 (C-4), 29.6 (C-5), 32.9 (C-3), 56.0 (OMe), 56.4 (C-6), 64.9 (CH_2OH), 68.2 (CHPh), 77.4 (NCH_2OMe), 110.3 (CHind), 115.8 (Cind), 118.6 (CHind), 120.3 (CHind), 122.8 (CHind), 125.6 (CHind), 127.4 (2 × CHind), 127.5 (CHind), 128.5 (2 × CHind), 137.1 (Cind), 137.6 (Cind), 172.5 (NCO); $[\alpha]_D^{22}$ = +25.5 (c 2.56, $CHCl_3$); MS-EI m/z 378 (M^+, 15), 347 (17), 258 (32), 241 (52), 210 (100), 200 (61), 168 (54), 106 (62); HMRS $C_{23}H_{27}N_2O_3$ (M^++1), 379.2016; found, 379.2020.

5.3. (3*R*,6*R*)-6-Allyl-3-ethyl-1-[(1*S*)-2-hydroxy-1-phenylethyl]-piperidin-2-one 9

Allyltrimethylsilane (0.83 mL, 5.18 mmol) was added to a cooled solution (0 °C) of **3**[12a] (635 mg, 2.59 mmol) in CH_2Cl_2 (10 mL). Then, $TiCl_4$ (9.1 mL of a 1 M solution in CH_2Cl_2, 9.1 mmol) was added dropwise in 2 h by a syringe pump. The reaction mixture was warmed up to rt and stirred for an additional 16 h. The mixture was poured onto ice, and the organic layer was separated, washed with brine, dried, filtered and concentrated. The residue was purified by column chromatography (1:1 to 4:1 EtOAc–hexane) to afford **9** (675 mg, 91%). IR (NaCl) 3387, 2952, 2874, 1617, 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 0.96 (m, 3H, CH_3), 1.64–1.73 (m, 3H, CH_2CH_3, H-4, H-5), 1.80 (m, 1H, CH_2CH_3), 1.87–2.00 (m, 2H, H-4, H-5), 2.20–2.34 (m, 2H, CH_2–CH=), 2.41 (m, 1H, H-3), 3.34 (m, 1H, H-6), 4.03 (dd, J = 12.0, 3.0 Hz, 1H, CH_2OH), 4.27 (m, 1H, CH_2OH), 4.51 (br s, 1H, OH), 4.63 (dd, J = 7.0, 3.0 Hz, 1H, CHAr), 5.04 (dd, J = 10.5, 1.0 Hz, =CH_2), 5.08 (m, 1H, =CH_2), 5.60 (m, 1H, CH=), 7.25–7.35 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.8 (CH_3CH_2), 20.9 (CH_2CH_3), 25.0 (C-5), 25.5 (C-4), 37.4 (CH_2–CH=), 43.1 (C-3), 57.8 (C-6), 64.5 (CH_2OH), 66.5 (CHAr), 118.0 (=CH_2), 127.4 (2 × CHAr), 127.5 (CHAr), 128.5 (2 × CHAr), 134.0 (CH=), 137.2 (C-*i*), 174.5 (NCO); $[\alpha]_D^{22}$ = −63.1 (c 1.25, $CHCl_3$). HMRS $C_{18}H_{26}NO_2$ (M^++1), 288.1958; found, 288.1958. Anal. Calcd for $C_{18}H_{25}NO_2 \cdot 1/4H_2O$: C, 74.06; H, 8.80; N, 4.80. Found: C, 74.20; H, 8.88; N, 4.71.

5.4. 3,3-Diallyl-1-[(1*S*)-2-hydroxy-1-phenylethyl]piperidin-2-one 10

$TiCl_4$ (8.0 mL of 1.0 M solution in CH_2Cl_2, 8.0 mmol) and Et_3SiH (0.80 mL, 5.0 mmol) were added dropwise to a cooled solution (0 °C) of **4**[15] (595 mg, 2.0 mmol) in anhydrous CH_2Cl_2 (7 mL). The mixture was allowed to warm up to rt, stirred for additional 18 h, and poured into ice. The combined organic layers were washed with 5% aqueous $NaHCO_3$ solution, dried and concentrated. The resulting residue was chromatographed (1:4 to 1:1 EtOAc–hexane) to give **10** (470 mg, 78%). IR (NaCl) 3398, 2939, 1611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 1.59–1.81 (m, 4H, H-4, H-5), 2.18 (td, J = 13.0, 8.0 Hz, 2H, CH_2–CH=), 2.54–2.67 (m, 2H, CH_2–CH=), 2.89 (m, 1H, H-6), 3.13 (m, 1H, H-6), 3.78 (br s, 1H, OH), 4.02 (m, 1H, CH_2OH), 4.14 (m, 1H, CH_2OH), 5.08–5.09 (m, 4H, =CH_2), 5.70–5.88 (m, 2H, CH=), 5.93 (dd, J = 9.0, 5.5 Hz, 1H, CHPh), 7.20–7.35 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.9 (C-5), 28.8 (C-4), 43.6 (C-6), 43.8 (CH_2–CH=), 43.9 (CH_2–CH=), 45.5 (C-3), 58.1 (CHAr), 61.1 (CH_2OH), 118.0 (=CH_2), 118.1 (=CH_2), 127.4 (CHAr), 127.6 (2 × CHAr), 128.4 (2 × CHAr), 134.2 (CH=), 134.4 (CH=), 137.1 (C-*i*), 175.4 (NCO); $[\alpha]_D^{22}$ = +1.4 (c 1.0, MeOH); MS-EI m/z 299 (M^+, 6), 268 (100), 257 (24), 240 (25), 180 (15), 91 (30); HMRS $C_{19}H_{26}NO_2$ (M^++1), 300.1958; found, 300.1955. Anal. Calcd for $C_{19}H_{25}NO_2 \cdot 1/2H_2O$: C, 73.99; H, 8.50; N, 4.54. Found: C, 74.12; H, 8.23; N, 4.30.

5.5. Na/liquid NH_3 debenzylation procedure: (5*S*,6*S*)-6-allyl-5-ethylpiperidin-2-one 14

Into a three-necked, round bottomed flask equipped with a cold-finger condenser charged with dry ice-acetone was condensed NH_3 (~150 mL) at −78 °C. The temperature was allowed to raise to −33 °C (reflux of liquid NH_3), and a solution of lactam **8**[4d] (1 g, 3.48 mL) in THF (5 mL) was added, followed by the addition of sodium metal in small portions until the dark blue colour persisted. After the mixture was stirred at -33 °C for 30 min, the reaction was carefully quenched by the addition of solid NH_4Cl until the blue colour disappeared. The mixture was stirred at rt overnight giving a white solid that was partitioned between water (50 mL) and CH_2Cl_2 (100 mL). The aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were dried, filtered and concentrated. The resulting residue was chromatographed (1:1 to 1:2 hexane–EtOAc) to give **14** as a white solid (470 mg, 81%) and starting lactam **8** (70 mg, 7%).

5.6. (5*S*,6*S*)-6-Allyl-5-ethylpiperidin-2-one 14

Table 1, entry 2. Freshly ground KOH (16.6 g, 296 mmol) was added to a solution of **8** (1.70 g, 5.92 mmol) in Et_2O (60 mL). The round- bottomed flask was equipped with a 1 gallon gas bag of O_2 and stirring was continued for 16 h at rt. The mixture was partitioned between H_2O and EtOAc. The aqueous phase was extracted with EtOAc (or CH_2Cl_2), and the combined organic phases were dried and concentrated. The resulting residue was purified by flash column chromatography (1:1 EtOAc–hexane) to yield **14** (790 mg, 80%). $[\alpha]_D^{22}$ = −23.7 (c 2.0, $CHCl_3$); HMRS $C_{10}H_{18}NO$ (M^++1), 168.1383; found, 168.1382.[4d]

Table 1, entry 4. Freshly ground NaOH (2.37 g, 59.2 mmol) was added to a solution of **8** (680 mg, 2.37 mmol) in THF (30 mL). The round bottomed flask was equipped with a 1 gallon gas bag of O_2 and a sun lamp, and stirring was continued for 24 h. The mixture was concentrated to dryness. Work up as above gave **14** (261 mg, 66%).

Table 1, entry 8. Freshly ground NaOH (400 mg, 10 mmol) was added to a solution of **8** (288 mg, 1 mmol) in MTBE (5 mL). The round bottomed flask was equipped with a 1 gallon gas bag of O_2 and the mixture was warmed at 40 °C for 16 h. Work up as above gave **14** (138 mg, 83%).

Table 2, entry 4. The reaction was performed from **8** (3.07 g, 10.67 mmol), NaOH (4.27 g, 106.7 mmol) and MTBE (22 mL) for 24 h. Work up as above gave **14** (1.51 g, 85%).

5.7. General procedure for the cleavage of the 2-hydroxy-1-phenylethyl moiety from lactams 5, 6, 7a, 9 and 10

In a round bottomed flask equipped with a 1 gallon gas bag of O_2, an excess (10–25 equiv) of freshly ground NaOH was added to a solution of lactam **5**, **6**, **7a**, **9**, or **10** (1 equiv) in MTBE (or THF). The mixture was heated at 40 °C and stirred slowly at this temperature for 24 h. The solvent was removed, and the residue was partitioned between H_2O and CH_2Cl_2. The combined organic phases were dried and concentrated to give the respective compounds **11–16**.

5.7.1. (*R*)-6-Methylpiperidin-2-one 11[4a]

Following the general procedure, from lactam **5** (70 mg, 0.30 mmol) and NaOH (600 mg, 15.0 mmol) in THF (15 mL) for 16 h, 48 mg of a 9:1 mixture of **11** and enamide **17** were obtained.[24] This crude mixture (48 mg) in Et_2O (25 mL) and 5 N aqueous H_2SO_4 acid (10 mL) was heated at reflux temperature for 1 h. The mixture was cooled and diluted with water (15 mL). The aqueous phase was neutralised to pH 7–8 with $NaHCO_3$ and extracted with EtOAc. The organic extracts were dried and concentrated. The residue was purified by column chromatography (1:1 hexane–EtOAc to EtOAc) to yield lactam **11**[4a] (30 mg, 87%). An analytical sample of **17** was obtained from the mixture by column chromatography (1:1 hexane–EtOAc to EtOAc) (*R*)-6-Methyl-1-(1-phenylvinyl)piperidin-2-one **17**: IR (NaCl) 2936, 1649 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 1.19 (d, J = 7.0 Hz, 3H, CH_3), 1.67 (m, 1H, H-5), 1.83 (m, 1H, H-4), 1.95–2.06 (m, 2H, H-4, H-5), 2.56 (m, 2H, H-3), 3.64 (dd, J = 11.2, 4.9 Hz, 1H, H-6), 5.22 (s, 1H, C=CH_2), 5.84 (s, 1H, C=CH_2), 7.31–7.38 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.4 (C-4), 20.6 (CH_3), 30.6 (C-5), 32.7 (C-3), 53.6 (C-6), 113.9 (=CH_2), 125.7 (2 × CHAr), 128.4 (CHAr), 128.5 (2 × CHAr), 136.1 (C-*i*), 145.3 (C=), 170.2 (NCO). MS-EI m/z 215 (M^+, 100), 186 (40), 172 (40), 118 (40), 103 (53), 77 (47), 55 (38).

5.7.2. (*S*)-6-Phenyl-2-piperidone 12

Following the general procedure, from lactam **6** (200 mg, 0.68 mmol) and NaOH (270 mg, 6.77 mmol) in THF (3.4 mL) for 24 h, compound **12**[25] (96 mg, 81%) was obtained.[26]

5.7.3. (6*S*)-6-[1-(Methoxymethyl)indol-3-yl]piperidin-2-one 13

Following the general procedure, from lactam **7a** (185 mg, 0.49 mmol) and NaOH (490 mg, 12.2 mmol) in MTBE (2.5 mL) for 24 h, compound **13** (91 mg, 72%) was obtained after column chromatography (99:1 to 98:2 CH_2Cl_2–MeOH). IR (KBr) 3241, 2953, 1662, 1081 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 1.83 (m, 1H, H-4), 1.90–2.03 (m, 2H, H-4, H-5), 2.20 (m, 1H, H-5), 2.49 (m, 2H, H-3), 3.25 (s, 3H, OCH_3), 4.91 (dd, J = 7.9, 4.6 Hz, 1H, H-6), 5.41 (d, J = 2.3 Hz, 2H, NCH_2OMe), 6.04 (br s, 1H, NH), 7.13 (s, 1H, H-2ind), 7.17 (t, J = 7.5 Hz, H-5ind), 7.28 (t, J = 7.9 Hz, 1H, H-6ind), 7.48 (d, J = 8.2 Hz, 1H, H-7ind), 7.59 (d, J = 7.9 Hz, 1H, H-4ind); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.6 (C-4), 30.0 (C-5), 31.4 (C-3), 50.6 (C-6), 56.0 (OMe), 77.4 (NCH_2OMe), 110.3 (C-7ind), 117.8 (C-3ind), 118.9 (C-4ind), 120.3 (C-5ind), 122.8 (C-6ind), 125.3 (C-2ind), 126.2 (C-3ind), 137.1 (C-7ind), 172.3 (NCO). $[\alpha]_D^{22} = -55.5$ (*c* 0.6, MeOH); MS-EI m/z 258 (M^+, 100), 227 (46), 188 (34), 157 (32), 130 (29); HMRS $C_{15}H_{19}N_2O_2$ (M^++1), 259.1441; found, 259.1443. Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.34. Found: C, 69.24; H, 7.04; N, 10.31.

5.7.4. (3*R*,6*R*)-6-Allyl-3-ethylpiperidin-2-one 15

Following the general procedure, from lactam **9** (200 mg, 0.70 mmol) and NaOH (280 mg, 7 mmol) in MBTE (3.5 mL) for 24 h, a 1:1 mixture of **15** and 3-*epi*-**15** (104 mg, 89%) was obtained. Epimers were separated by column chromatography (4:1 to 1:1 hexane–EtOAc). **15.** IR (NaCl) 3204, 2935, 1663, 1459 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 0.94 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.66–1.80 (m, 3H, H-4, 2 × H-5), 1.85 (m, 1H, CH_2CH_3), 2.07–2.30 (m, 3H, H-3, H-5, 2 × CH_2–CH=), 3.37 (m, 1H, H-6), 5.10 (m, 2H, =CH_2), 5.13 (m, 2H, =CH_2), 5.70 (m, 1H, CH=), 6.11 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.8 (CH_2CH_3), 22.8 (C-4), 24.7 (CH_2CH_3), 25.0 (C-5), 41.1 (CH_2–CH=), 41.7 (C-3), 51.7 (C-6), 118.8 (=CH_2), 133.4 (=CH), 175.4 (NCO); $[\alpha]_D^{22} = +20.1$ (*c* 0.63, MeOH); HMRS $C_{10}H_{18}NO$ (M^++1), 168.1383; found, 180.1382. Anal. Calcd for $C_{10}H_{17}NO{\cdot}1/4H_2O$: C, 69.93; H, 10.27; N, 8.16. Found: C, 69.80; H, 10.25; N, 7.98. (3*S*,6*R*)-6-Allyl-3-ethyl-2-piperidin-2-one 3-*epi*-**15**. IR (NaCl) 3211, 2933, 1656, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 0.93 (m, J = 7.5 Hz, 3H, CH_2CH_3), 1.39–1.48 (m, 2H, H-4, H-5), 1.56 (m, 1H, CH_2CH_3), 1.90–1.98 (m, 3H, H-4, H-5, CH_2CH_3), 2.09 (m, 1H, CH_2–CH=), 2.18 (m, 1H, H-3), 2.32 (m, 1H, CH_2–CH=), 3.37 (m, 1H, H-6), 5.14 (m, 1H, =CH_2), 5.18 (m, 1H, =CH_2), 5.71 (m, 1H, CH=), 5.78 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.0 (CH_2CH_3), 24.1 (CH_2CH_3), 25.4 (C-4), 28.9 (C-5), 41.5 (CH_2–CH=), 42.2 (C-3), 52.3 (C-6), 119.1 (=CH_2), 133.3 (=CH), 174.5 (NCO); $[\alpha]_D^{22} = -5.4$ (*c* 0.7, MeOH); MS-EI m/z 168 (M^++1, 1), 126 (100), 98 (9), 83 (69), 55 (29); HMRS $C_{10}H_{18}NO$ (M^++1), 168.1383; found, 180.1381.

5.7.4.1. Epimerisation. Freshly ground NaOH (72 mg, 1.79 mmol) was added under an inert atmosphere to a solution of **15** (30 mg, 0.18 mmol) in MTBE (1 mL) and the mixture was heated at 40 °C for 24 h. The solvent was evaporated and the residue was partitioned between H_2O and CH_2Cl_2. The combined organic extracts were washed with aqueous NH_4Cl, dried and evaporated to give a 1:1 mixture of **15** and 3-*epi*-**15** (23 mg, 77%).

5.7.5. 3,3-Diallylpiperidin-2-one 16

Following the general procedure, from lactam **10** (150 mg, 0.5 mmol) and NaOH (200 mg, 5.0 mmol) in MTBE (2.5 mL) for 24 h, compound **16** (80 mg, 88%) was obtained after column chromatography (1:1 EtOAc–hexanes to EtOAc). IR (NaCl) 3214, 3074, 2936, 1657, 1489 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 1.66–1.77 (m, 4H, H-4, H-5), 2.15 (dd, J = 13.5, 8.0 Hz, 2H, CH_2–CH=), 2.49 (ddd, J = 13.5, 8.0, 1.0 Hz, 2H, CH_2–CH=), 3.21 (m, 2H, H-6), 5.02 (m, 2H, =CH_2), 5.06 (m, 2H, =CH_2), 5.70–5.81 (m, 2H, CH=), 6.59 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.4 (C-5), 28.8 (C-4), 42.5 (C-6), 42.7 (2 × CH_2–CH=), 44.7 (C-3), 118.0 (2 × =CH_2), 134.2 (2 × =CH), 176.3 (NCO); HMRS $C_{11}H_{18}NO$ (M^++1), 180.1383; found, 180.1383.

5.8. (*R*)-1-Benzoyl-6-methylpiperidin-2-one 18[21]

6-Methylpiperidone **11** (100 mg, 0.75 mmol) in THF (1 mL) was added via cannula to a solution of *n*-BuLi (0.54 mL of a 1.6 M solution in hexane, 0.86 mmol) in THF (1 mL) at −78 °C. After stirring at −78 °C for 1.5 h, benzoyl chloride (87 μL, 0.75 mmol) was added dropwise. The mixture was slowly warmed to rt and stirred for 19 h. Then, the yellowish suspension was poured into a saturated NH_4Cl solution (5 mL) and extracted with Et_2O. The combined organic layers were dried and concentrated, and the resulting residue was chromatographed (9:1 to 1:1 hexane–EtOAc) to afford **18**, which was crystallised from hexane–EtOAc to give a white solid (80 mg, 53%). IR (NaCl) 2953, 1675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 1.81 (m, 1H, H-5), 1.90 (m, 1H, H-4), 2.02–2.56 (m, 2H, H-4, H-5), 2.52–2.56 (m, 2H, H-3), 4.53 (m, 1H, H-5), 7.36–7.40 (m, 2H, ArH), 7.44 (m, 1H, ArH), 7.54–7.56 (m, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.8 (C-4), 20.3 (CH_3), 29.4 (C-5), 34.2 (C-3), 51.6 (C-6), 127.8 (2 × CHAr), 128.2 (2 × CHAr), 131.6 (CHAr), 136.4 (C-*i*), 174.0 (NCO), 174.5 (NCO); mp = 74–76 °C (hexane–EtOAc); HMRS $C_{13}H_{16}NO_2$ (M^++1), 218.1176; found, 218.1174.

Acknowledgements

We thank Dr. Pavel Mach (Comenius University of Bratislava) for fruitful discussions. Financial support from the Ministry of Science and Innovation, Spain (Project CTQ2009-07021/BQU), and the AGAUR, Generalitat de Catalunya (Grant 2009-SGR-111) is gratefully acknowledged. Thanks are also due to the Ministry of Education and Science for fellowships to V.S. and C.A.

References

1. Chiral nonracemic amino alcohol-derived bicyclic lactams were initially studied by Meyers. For reviews, see: (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503–9569; (b) Meyers, A. I.; Brengel, G. P. *Chem. Commun.* **1997**, 1–8; (c) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843–9873.
2. Coombs, T. C.; Lee, M. D., IV; Wong, H.; Armstrong, M.; Cheng, B.; Wenyong, C.; Moretto, A. F.; Liebeskind, L. S. *J. Org. Chem.* **2008**, *73*, 882–888.
3. For a review on chiral oxazolopiperidone lactams and their role in the synthesis of natural products, see: Escolano, C.; Amat, M.; Bosch, J. *Chem. Eur. J.* **2006**, *12*, 8198–8207.
4. (a) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919–1928; (b) Amat, M.; Pérez, M.; Llor, N.; Escolano, C.; Luque, F. J.; Molins, E.; Bosch, J. *J. Org. Chem.* **2004**, *69*, 8681–8693; (c) Amat, M.; Pérez, M.; Minaglia, A. T.; Casamitjana, N.; Bosch, J. *Org. Lett.* **2005**, *7*, 3653–3656; (d) Amat, M.; Escolano, C.; Gómez-Esqué, A.; Lozano, O.; Llor, N.; Griera, R.; Molins, E.; Bosch, J. *Tetrahedron: Asymmetry* **2006**, *17*, 1581–1588; (e) Amat, M.; Pérez, M.; Minaglia, A. T.; Peretto, B.; Bosch, J. *Tetrahedron* **2007**, *63*, 5839–5848; (f) Amat, M.; Pérez, M.; Minaglia, A. T.; Bosch, J. *J. Org. Chem.* **2008**, *73*, 6920–6923; (g) Amat, M.; Pérez, M.; Minaglia, A. T.; Passarella, D.; Bosch, J. *Tetrahedron: Asymmetry* **2008**, *19*, 2406–2410; (h) Amat, M.; Pérez, M.; Proto, S.; Gatti, T.; Bosch, J. *Chem. Eur. J.* **2010**, *16*, 9438–9441; (i) Amat, M.; Elias, V.; Llor, N.; Subrizi, F.; Molins, E.; Bosch, J. *Eur. J. Org. Chem.* **2010**, 4017–4026.
5. Cleavage of 2-hydroxy-1-phenylethyl moiety from chiral oxazolopyrrolidone lactams derived from (*R*)-phenylglycinol has been performed by a multistep sequence involving the formation of the corresponding phenylenamide derivative and acid hydrolysis: (a) Ennis, M. D.; Hoffman, R. L.; Ghazal, N. B.; Old, D. W.; Mooney, P. A. *J. Org. Chem.* **1996**, *61*, 5813–5817; (b) Nyzam, V.; Belaud, C.; Zammattio, F.; Villieras, J. *Tetrahedron: Asymmetry* **1996**, *7*, 1835–1843; (c) Fains, O.; Vernon, J. M. *Tetrahedron Lett.* **1997**, *38*, 8265–8266; (d) Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1999**, *40*, 141–142; (e) Agami, C.; Couty, F.; Evano, G. *Tetrahedron Lett.* **1999**, *40*, 3709–3712; (f) Nieman, J. A.; Ennis, M. D. *Org. Lett.* **2000**, *2*, 1395–1397; (g) Bragg, R. A.; Clayden, J.; Bladon, M.; Ichihara, O. *Tetrahedron Lett.* **2001**, *42*, 3411–3414; (h) Newhouse, B.; Allen, S.; Fauber, B.; Anderson, A. S.; Eary, C. T.; Hansen, J. D.; Schiro, J.; Gaudino, J. J.; Laird, E.; Chantry, D.; Eberhardt, C.; Burgess, L. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5537–5542; (i) Chen, M.-D.; Zhou, X.; He, M.-Z.; Ruan, Y.-P.; Huang, P.-Q. *Tetrahedron* **2004**, *60*, 1651–1657; (j) Hansen, J. D.; Newhouse, B. J.; Allen, S.; Anderson, A.; Eary, T.; Schiro, J.; Gaudino, J.; Laird, E.; Allen, A. C.; Chantry, D.; Eberhardt, C.; Burguess, L. E. *Tetrahedron Lett.* **2006**, *47*, 69–72; (k) Zuo, Z.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2010**, *132*, 13226–13228.
6. For other debenzylation methods for amides, see: TFA: (a) Schlessinger, R. H.; Bebernitz, G. R.; Lin, P.; Poss, A. Y. *J. Am. Chem. Soc.* **1985**, *107*, 1777–1778; (b) Shimshock, S. J.; Waltermire, R. E.; Deshong, P. *J. Am. Chem. Soc.* **1991**, *113*, 8791–8796; O_2, *n*-BuLi: (c) Williams, R. M.; Kwast, E. *Tetrahedron Lett.* **1989**, *30*, 451–454; MsOH: (d) Paik, S.; Lee, J. Y. *Tetrahedron Lett.* **2006**, *47*, 1813–1815; Radical conditions (e) Baker, S. R.; Parsons, A. F.; Wilson, M. *Tetrahedron Lett.* **1998**, *39*, 331–332; *p*-TsOH: (f) Chern, C.-Y.; Huang, Y.-P.; Kan, W. M. *Tetrahedron Lett.* **2003**, *44*, 1039–1041.
7. Joshi, D. K.; Sutton, J. W.; Carver, S.; Blanchard, J. P. *Org. Process Res. Dev.* **2005**, *9*, 997–1002.
8. Gangopadhyay, R. K.; Das, S. K. *Process Saf. Prog.* **2008**, *27*, 15–20.
9. Gigg, R.; Conant, R. *J. Chem. Soc., Chem. Commun.* **1983**, 465–466.
10. Haddach, A. A.; Kelleman, A.; Deaton-Rewolinski, M. V. *Tetrahedron Lett.* **2002**, *43*, 399–402.
11. García-Valverde, M.; Pedrosa, R.; Vicente, M. *Synlett* **2002**, 2092–2094.
12. (a) Amat, M.; Pshenichnyi, G.; Bosch, J.; Molins, E.; Miravitlles, C. *Tetrahedron: Asymmetry* **1996**, *7*, 3091–3094; (b) Amat, M.; Bosch, J.; Hidalgo, J.; Cantó, M.; Pérez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074–3084. and references therein.
13. Amat, M.; Llor, N.; Hidalgo, J.; Bosch, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2237–2240.
14. (a) Amat, M.; Escolano, C.; Llor, N.; Huguet, M.; Pérez, M.; Bosch, J. *Tetrahedron: Asymmetry* **2003**, *14*, 1679–1683; b See also Ref. 4d
15. Amat, M.; Lozano, O.; Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 4431–4439.
16. Amat, M.; Llor, N.; Bosch, J.; Solans, X. *Tetrahedron* **1997**, *53*, 719–730.
17. The use of $LiOH.H_2O$ proved fruitless.
18. The use of DMSO as the solvent proved fruitless.
19. (a) Santamaria, J.; Jroundi, R.; Rigaudy, J. *Tetrahedron Lett.* **1989**, *30*, 4677–4680; (b) Refs. 10 and 11 and references therein.
20. When the reaction was carried out in THF the yields were 88% (**11**) and 12% (**17**).
21. (a) Foti, C. J.; Comins, D. L. *J. Org. Chem.* **1995**, *60*, 2656–2657; (b) Filippis, A.; Gómez Pardo, D.; Cossy, J. *Synthesis* **2004**, 2930–2933.
22. (a) Voronenkov, V. V.; Vinogradov, A. N.; Belyaev, V. A. *Russ. Chem. Rev.* **1970**, *39*, 944–952; (b) Crabtree, R. H.; Habib, A.. In *Comprehensive Organic Synthesis*; Trost, B. H., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 7, p 10.
23. For examples of the oxidation of enamines with oxygen, see: (a) Huber, J. E. *Tetrahedron Lett.* **1968**, *9*, 3271–3272; (b) Foote, C. S.; Dzakpasu, A. A.; Lin, J. W.-P. *Tetrahedron Lett.* **1975**, *16*, 1247–1250; (c) Wasserman, H. H.; Terao, S. *Tetrahedron Lett.* **1975**, *16*, 1735–1738; (d) Fetter, J.; Lempert, K.; Mølleer, J. *Tetrahedron* **1978**, *34*, 2557–2563; (e) Curtis, N. M.; Gorman, A. A.; Prescott, A. L. *J. Am. Chem. Soc* **1988**, *110*, 7549–7550; (f) Chang, Y.-G.; Kim, K. *Synlett* **2002**, 1423–1426.
24. When reaction was performed in MTBE in the presence of a sun lamp for 44 h, the yield and ratio of **11** and **17** were coincident with that described in the Section 5.7.1.
25. Kawęcki, R. *Tetrahedron* **2001**, *57*, 8385–8390.
26. When reaction was carried out in DMSO instead of THF, lactam **12** was isolated in 41% yield. The ^{1}H NMR of the crude reaction mixture showed representative peaks of the corresponding enamide of **12**: 5.02 (s, 1H, $=CH_2$) and 5.51 (s, 1H, $=CH_2$). MS-EI *m*/*z* 277 (M^++1, 91), 248 (100), 130 (89), 104 (58), 91 (51).